DOCUMENT RESUME

ED 293 068 CG 020 716

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TITLE Useful Information on...Alzheimer's Disease.
INSTITUTION National Inst. of Mental Health (DHHS), Rockville, MD.
PUB DATE 87
NOTE 18p.; This publication was made possible by the American Association for Geriatric Psychiatry.
PUB TYPE Reports - General (140)

EDRS PRICE MF01/PC01 Plus Postage.
DESCRIPTORS *Aging (Individuals); *Clinical Diagnosis; *Etiology; *Mental Disorders; *Older Adults
IDENTIFIERS *Alzheimers Disease

ABSTRACT

This brochure provides information on Alzheimer's disease by examining who gets Alzheimer's disease and what to expect when someone has Alzheimer's disease. Abnormal brain tissue findings are discussed and three clinical features of Alzheimer's disease are listed: dementia; insidious onset of symptoms; and exclusion of all other specific causes of dementia as determined by history, physical examination, laboratory tests, and psychometric and other studies. Diagnosis by exclusion is explained and the importance of a comprehensive clinical evaluation which includes a thorough general medical workup, a neurological examination, and a psychiatric evaluation is emphasized. A section on the search for the cause of Alzheimer's disease briefly explains five prominent theories about the cause: (1) the blood vessel theory; (2) the slow virus theory; (3) the autoimmune theory; (4) chemical theories involving deficiencies and toxic excesses; and (5) the genetic theory. Treatment of Alzheimer's disease is discussed and hope for the future through research is described. (NB)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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National Institute of Mental Health

Useful Information On . . .

Alzheimer's Disease

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U.S. DEPARTMENT OF HEALTH AND
HUMAN SERVICES
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Introduction

Alzheimer's Disease (AD) is *not* a normal part of aging. It is not something that inevitably happens in later life. Rather, it is a *disease* of unknown cause that affects a small but significant percentage of people 65 years and older.

AD is the exception, rather than the rule, in old age. Only 5 to 6 percent of older people develop AD—but this means approximately 2 million Americans are affected. At least half the people in U.S. nursing homes have AD or a related disorder, incurring costs in excess of 20 billion dollars annually.

It is important to learn about AD because, although the disorder is not curable or reversible, there are ways to alleviate symptoms and suffering and assist families.

Among the terms that have been used to describe AD have been senile dementia, SDAT (senile dementia of the Alzheimer type), presenile dementia (when the disorder has its onset prior to age 65), primary degenerative dementia, organic brain syndrome (OBS), and senility. "Senility" is not a medical term; it is nonspecific and misleading. Often, it has been used to describe AD and a range of *reversible* problems either misdiagnosed as AD or inappropriately dismissed as being untreatable.

Who Gets Alzheimer's Disease?

A family pattern of AD has been described by various investigators, suggesting that heredity may influence its development. Other researchers, however, emphasize that we know little about the genetic aspects of the disorder. A genetic basis, at least with a *small subgroup* of families where the disease has more frequently occurred, has been identified through the discovery of a genetic marker on chromosome 21 in those particular families. At the same time, data indicate that the likelihood of a close relative (sibling, child, or parent) of an afflicted individual developing AD is low. In most cases, such an individual's risk is only slightly higher than that of someone in the general population, where the

lifetime risk is below 1 percent. It should also be pointed out that many disorders have a genetic potential which is never expressed—that is, despite being at risk for a certain illness, one might go through life without the disease ever developing. In other instances, a genetic potential for a certain disorder may be released *only* if it is triggered by other risk factors. There have been a few reports of a possible association between serious head injuries and the later onset of AD, but otherwise no other risk factors have been unequivocally identified for AD.

What To Expect When Someone Has Alzheimer's Disease

The onset of AD is usually very slow and gradual, rarely occurring before age 65. Over time, however, it follows a progressively more serious course. Among the various symptoms that typically develop, none is unique to AD. Many other conditions—both physical and psychological—can mimic AD at its various stages. It is therefore essential for suspicious changes to be thoroughly evaluated before they become inappropriately or negligently labeled Alzheimer's disease.

Problems of memory, particularly recent or short-term memory, are common early in the course of the disease. For example, the individual may, on repeated occasions, forget to turn off the oven or may not recall which of the morning's medicines were taken. Mild personality changes, such as less spontaneity or a sense of apathy and a tendency to withdraw from social interactions, occur early in the illness. As the disease progresses, problems in abstract thinking or in intellectual functioning develop. The individual may begin to have trouble with figures when working on bills, with understanding what is being read, or with organizing the day's work. Further disturbances in behavior and appearance may also be seen at this point, such as agitation, irritability, quarrelsomeness, and less ability to dress appropriately. Later in the course of the disorder, the affected individuals may become confused or disoriented about what month or year it is and be unable to describe accurately where they live

or to name correctly a place being visited. Eventually they may wander, be unable to engage in conversation, seem inattentive and erratic in mood, appear uncooperative, lose bladder and bowel control, and, in extreme cases, become totally incapable of caring for themselves if the final stage is reached. Death then follows, perhaps from pneumonia or some other problem that occurs in severely deteriorated states of health. The average course of the disease from onset to death is about 8 to 10 years, but it may range from under 2 to over 20 years. Those who develop the disorder later in life may die from other illnesses (such as heart disease) before AD reaches its final and most serious stage.

Though the changes just described represent the general range of symptoms for AD, the specific problems, along with the rate and severity of decline, can vary considerably with different individuals. Indeed, most persons with AD can function at a reasonable level and remain at home far into the course of the disorder. Moreover, throughout much of the course of the illness individuals maintain the capacity for giving and receiving love, for sharing warm interpersonal relationships, and for participating in a variety of meaningful activities with family and friends.

A person with AD may no longer be able to do math, but still be able to read a magazine with pleasure for months or years to come. Playing the piano might become too stressful in the face of increasing mistakes, but singing along with others may still be satisfying. The chess board may have to be put away, but one may still be able to play tennis. Thus, despite the many exasperating moments in the lives of Alzheimer patients and their families, many opportunities remain for positive interactions. Challenge, frustration, closeness, anger, warmth, sadness, and satisfaction may all be experienced by those who work to help the person with AD cope as best as possible with the disease.

The reaction of an individual to the illness—his or her capacity to cope with it—also varies, depending on such factors as lifelong personality patterns and the nature and severity of stress in the immediate environment. Depression, severe

uneasiness, and paranoia or delusions may accompany or result from the disease, but they can often be alleviated by appropriate treatments. *Although there is no cure for AD, treatments are available to alleviate the symptoms which cause suffering.*

Abnormal Brain Tissue Findings

Microscopic brain tissue changes have been described in Alzheimer's disease since Alois Alzheimer first reported them in 1906. These are the *plaques and tangles* — senile or neuritic plaques (degenerating nerve cells combined with a form of protein called amyloid) and neurofibrillary tangles (nerve cell malformations). The brains of AD patients of all ages reveal these findings on autopsy examinations.

Computer-Assisted Tomography (CAT Scan) changes become more evident as the disease progresses — not necessarily early on. Thus a CAT Scan performed in the first stages of the disease cannot in itself be used to make a definitive diagnosis of AD; its value is in helping to establish whether certain disorders (some reversible) that mimic AD are present. Later on, CAT Scans often reveal changes characteristic of AD, namely an atrophied (shrunken) brain with widened sulci (tissue indentations) and enlarged cerebral ventricles (fluid chambers).

As research on AD progresses, scientists are describing other abnormal anatomical and chemical changes associated with the disease. These include nerve cell degeneration in the brain's nucleus basalis of Meynert and reduced levels of the neurotransmitter acetylcholine in the brains of AD victims. But from a practical standpoint, the "classical" *plaque and tangle* changes seen at autopsy typically suffice for a diagnosis of AD based on brain tissue changes. In fact, it is *only* through the study of brain tissue from a person who was thought to have AD that a definitive diagnosis of the disorder can be made.

Clinical Features of Alzheimer's Disease

The "clinical" features of AD, as opposed to the "tissue" changes, are threefold:

1. Dementia — significant loss of intellectual abilities such as memory capacity, severe enough to interfere with social or occupational functioning;
2. Insidious onset of symptoms — subtly progressive and irreversible course with documented deterioration over time;
3. Exclusion of all other specific causes of dementia — by history, physical examination, laboratory tests, psychometric and other studies.

Diagnosis By Exclusion

Based on these criteria, the clinical diagnosis of AD has been referred to as a diagnosis by exclusion, and one that can only be made in the face of clinical deterioration over time. There is no specific clinical test or finding that is unique to AD. Hence, all disorders that can bring on similar symptoms must be systematically excluded or "ruled out." This explains why diagnostic workups of individuals where the question of AD has been raised can be so frustrating to patient and family alike; they are not told that AD has been specifically diagnosed, but that other possible diagnoses have been dismissed, leaving AD as the likely diagnosis by the process of elimination.

Scientists hope to develop one day a specific test for AD, based on a specific laboratory or genetic finding ("marker"). Some think that the results from genetic research may lead to a diagnostic marker for certain persons evaluated for AD. Other research has led to preliminary reports that a protein known as "ALZ 68" observed in the brains and cerebrospinal fluid of those with AD may have potential diagnostic value. Still, a specific diagnostic marker for AD is not yet available.

Meanwhile, AD is the most overdiagnosed and misdiagnosed disorder of mental functioning in older adults. Part of the problem, already alluded to, is that many other disorders show symptoms that resemble those of AD. The crucial difference, though, is that many of these disorders—unlike AD—may be stopped, reversed, or cured with appropriate treatment. But first they must be identified, not dismissed as Alzheimer's disease or senility.

Conditions that affect the brain and result in intellectual, behavioral, and psychological dysfunction are referred to as Organic Mental Disorders. These disorders represent a broad grouping of diseases and include AD. Organic mental disorders that can cause clinical problems like those of AD, but which might be reversible or controlled with proper diagnosis and treatment, include the following:

Side Effects of Medications: Unusual reactions to medications, too much or too little of prescribed medications, combinations of medications which, when taken together, cause adverse side effects.

Substance Abuse: Abuse of legal and/or illegal drugs, alcohol abuse.

Metabolic Disorders: Thyroid problems, nutritional deficiencies, anemias, etc.

Circulatory Disorders: Heart problems, strokes, etc.

Neurological Disorders: Normal-pressure hydrocephalus, multiple sclerosis, etc.

Infections: Especially viral or fungal infections of the brain.

Trauma: Injuries to the head.

Toxic Factors: Carbon monoxide, methyl alcohol, etc.

Tumors: Any type within the skull—whether originating or metastasizing there.

In addition to organic mental disorders resulting from these diverse causes, other forms of mental dysfunction or mental health problems can also be confused with AD. For example, a severe form of depression, referred to as "pseudodementia," can cause problems with memory and concentration that initially may be indistinguishable from early symptoms of AD. But pseudodementia, like depression in general, can be reversed. Other psychiatric problems can similarly masquerade as AD, and, like depression, respond to treatment.

Of course, not all memory changes or complaints in later life signal AD or mental disorder. Many memory changes are only temporary, such as those that occur with bereavement or any stressful situation that makes it difficult to concentrate. In fact, older people are often accused or accuse themselves of memory changes which are not really taking place. If a person in his thirties misplaces keys or a wallet, forgets the name of a neighbor, or calls one sibling by another's name, nobody gives it a second thought. But the same normal forgetfulness for people in their seventies may raise unjustifiable concern. On the other hand, serious memory difficulties should not be dismissed as an unavoidable part of normal aging. Since rigorous studies on intelligence in later life show that healthy people who stay intellectually active maintain a sharp mind throughout the life cycle, noticeable decline in older adults that interferes with functioning should be clinically explored for an underlying problem.

The Importance of a Comprehensive Clinical Evaluation

Because of the many other disorders that can be confused with Alzheimer's disease, a comprehensive clinical evaluation is essential to arrive at a correct diagnosis of symptoms that look like those of AD. Such an assessment should include at least three major components—(1) a thorough general medical workup, (2) a neurological examination, and (3) a psychiatric evalua-

tion that may include psychological or psychometric testing. The family physician can be consulted about the best way to get the necessary examinations.

The Search for the Cause of Alzheimer's Disease

Alzheimer's disease has emerged as one of the great mysteries in modern day medicine, with many clues but no answers as to its cause. The quest to uncover its cause has the air of a veritable whodunit saga. Though none of the leading theories about the genesis of AD has resolved the mystery, each has led to certain intriguing findings that suggest further investigation is needed. It is important to examine these theories, not only to understand current thinking on AD, but also to learn what popular ideas have proved to be incorrect. There have been at least five prominent theories about the cause of AD:

1 *The Blood Vessel Theory*

Defects in blood vessels supplying blood to the brain have been studied as a possible cause of AD. Hardening of the brain's arteries, also known as cerebroarteriosclerosis, proved *not* to be a cause of AD. Thus, the hyperbaric oxygen chamber treatment for it proved ineffective. Stroke, another blood vessel problem that occurs later in life, can cause symptoms like those of AD. But this condition, called multi-infarct dementia, differs from AD. More recently, the blood vessel theory has been expanded to hypothesize potential defects in the *blood-brain barrier*, a protective membrane-like mechanism that guards the brain from foreign bodies or toxic agents circulating in the blood stream outside the brain.

2 *The Slow Virus Theory*

Because a slow acting virus has been identified as a cause of some brain disorders (for example, Creutzfeldt-Jakob disease) that closely resemble Alzheimer's disease, a *slow virus* has been postulated in AD.

While various researchers have suggested that suspicious brain tissue changes in AD victims may be caused by a virus, to date a virus has *not* been isolated from the brains of those with AD.

3 *The Autoimmune Theory*

The body's immune system, which protects against potentially harmful foreign invaders, may erroneously begin to attack its own tissues, producing antibodies to its own essential cells. This is called an *autoimmune* response, and it may take place in the brain. Some scientists speculate that certain late life changes in aging neurons (the major nerve cells of the brain) might be triggering an autoimmune response that evokes symptoms of AD in vulnerable individuals. Curiously, some anti-brain antibodies have been identified in the brains of those with AD. Their significance, though, is not known, especially since some anti-brain antibodies have also been identified in aging brains without AD. Moreover, even if changes are occurring in brain neurons to trigger an autoimmune response, what originally induces these brain cell changes is not known.

4 *Chemical Theories (Deficiencies and Toxic Excesses)*

A. Chemical Deficiencies: One of the ways in which brain cells communicate with one another is through chemicals called neurotransmitters. Studies of AD brains have uncovered diminished levels of various neurotransmitters that are thought to influence intellectual functioning and behavior. For example, reduced levels of the neurotransmitter acetylcholine (ACh) have been found in AD, and this has been coupled with observations that drugs whose side effects lower ACh levels in the brain can cause reversible memory problems. These findings have led to a number of drug studies employing pharmacologic agents to elevate ACh in AD patients. Such drugs have included lecithin, choline, physostigmine, THA (tetrahydroaminoacridine), and others, used alone or in different combinations with one another. The results of these experiments are difficult to inter-

pret. In some of these studies, a few AD patients seem to show *minor* improvement, over a *brief* but not sustained period of time. Typically, any improvement may be on certain narrow test measures—and not usually on significant activities of daily living which would be more important to the person's family and physician. Nonetheless, the researchers' enthusiasm is understandable, for they are dealing with the *potential modifiability* of underlying physiological phenomena that influence the AD symptoms. The drugs they are studying now may not be the right ones, but they may point the way to the discovery of more effective pharmacologic agents.

B. Toxic Chemical Excesses: Although some researchers have found increased levels of aluminum in the brains of AD victims, others have not. And while some investigators have hypothesized that aluminum may play a role in the genesis of AD, most have regarded aluminum as an *effect* of the disorder rather than its *cause*. In other words, instead of aluminum acting to induce brain tissue changes in AD, it more likely accumulates in response to such changes. Research continues in an effort to better understand this phenomenon.

5 *The Genetic Theory*

Genetic aspects of AD are confusing. For example, a disorder can occur more frequently in certain families than in others, but still not be genetic. Since family members living together are exposed to the same environment, they would all be at increased risk if an environmental toxin or infectious agent were the causative factor in AD. Furthermore, a disorder can be congenital and not hereditary—that is, prenatal problems can cause developmental defects not brought on by heredity. And, as already mentioned, an illness can be hereditary, but remain in a latent state if some other disease factor does not occur to trigger its onset.

Genetic interest in AD was stirred by the discovery of an apparent association between Alzheimer's disease and Down's syndrome in certain families. Although a clear understanding of

this finding remains elusive, it has led to efforts to identify a genetic marker for AD on Chromosome 21, because this is the same chromosome that is affected in Down's syndrome.

Despite the identification of a genetic marker on chromosome 21 in that small number of families where AD has occurred with unusual frequency, the extent of genetic and hereditary involvement in AD remains unclear. There are a vast number of people affected with this disorder who are not part of a strong family pattern, and this has led some investigators to postulate that there may be a number of different subtypes of AD, with different risk factors and causes.

Treatment

Two critical crossroads reached in the approach to treatment for Alzheimer's disease were (1) the recognition of AD as a *disorder* distinct from the normal aging process, and (2) the realization that in developing therapeutic and social interventions for a major illness or disability the concept of *care* can be as important as that of cure.

Moreover, in addition to the symptoms of AD mentioned earlier, other symptoms and aggravating factors may compound the problem. Patient, environmental, and family stresses can converge to exaggerate the patient dysfunction and family burden during the clinical course of AD. Identifying these stresses and making appropriate changes can provide the foundation for more effective treatment and fewer everyday problems.

In the AD patient, depression or delusions can aggravate dysfunction. These problems, which emerge during the course of the disorder in some individuals with AD, compound memory impairment; they make the affected individual do worse than what would be expected from the dementia alone — causing clinical conditions referred to as "excess disability" states. Depression by itself can mimic dementia, as in pseudodementia. When combined with dementia, depression exacts yet greater incapacity and suffering in the AD patient. Depression in AD can respond if treated. Indeed this highlights one of the truly

extraordinary phenomena that can be observed in AD. By alleviating an excess disability state, actual clinical improvement can result — even though the underlying pathological process is advancing. In other words, at a given point in time, the patient's symptoms can be reduced, suffering lowered, capacity to cope buttressed, with family burden eased as a further result. These are traditional goals of treatment for all illnesses.

The patient's immediate environment can similarly interfere with coping, adding to the level of impairment. Modifying one's surroundings can reduce stresses imposed by environmental factors. There is the matter of safety, as in the need to protect the person from wandering toward a stairway and subsequently falling. There is the matter of lowering the frustration level, such as placing different cues in the immediate environment to combat memory loss and to reduce resulting stress and disorganization. There is the matter of finding the most protective but least restrictive setting for care which at some point may involve a move away from home to a nursing home or other care facility well-equipped to deal with those who have AD.

Stress on the family can take a toll on patient and caregiver alike. If burden mounts it not only places the mental health of family caregivers at risk, it also diminishes their ability to provide care to the AD patient. Hence, assistance to the family as a whole must be considered.

As the disease progresses, families often experience tremendous stress and pain at seeing unsettling changes in a loved one, and they commonly feel guilt over not being able to do enough. The prevalence of reactive depression among family members in this situation is disturbingly high.

The likelihood, intensity, and duration of depression among caregivers can all be lowered through available interventions. For example, to the extent that family members can offer emotional support to each other and perhaps seek professional consultation, they will be better prepared in helping their loved one manage the illness and in coming to know the limits of what they themselves can reasonably do.

Since the components of the problem vary, so too should the focus, nature, and sources of interventions. Interventions should focus on the patient's symptoms, the affected individual's everyday environment, and the family support system. Specific interventions can involve support from the family, the help of a homemaker or other aide in the home, employment of behavioral therapies, and the use of medication. The sources for interventions can range from family support groups such as those available through the *Alzheimer's Disease and Related Disorders Association (ADRDA)*, to professional consultations for the patient and family such as with a mental health specialist, to a variety of community programs such as day or respite care. Information on what assistance is available in a given community can be gained by contacting the local Office on Aging or a federally funded Area Agency on Aging, a Community Mental Health Center or local Medical Society, or a nearby Local Chapter of ADRDA.

Though AD cannot at present be cured, reversed, or stopped in its progression, much can be done to help both the patient and the family live through the course of the illness with greater dignity and less discomfort. Toward this goal, appropriate clinical interventions and community services should be vigorously sought.

Hope For The Future, Through Research

While Alzheimer's disease remains a mystery, with its cause and cure not yet found, there is considerable excitement and hope about new findings that are unfolding in numerous research settings. The connecting pieces to the puzzle called *Alzheimer's disease* continue to be found. At the same time, there are more and more partners involved in the effort, with growing national and international interest. Government, industry, academia, and the volunteer sector are all becoming more and more active; federal, State, community, corporate, and foundation support for new studies and better services are all on the rise.

At the federal level, in addition to the National Institute of Mental Health, several other key agencies have programs that are important to AD. These include: The National Institute on Aging, the National Institute of Neurological and Communicative Disorders and Stroke, the National Institute of Allergy and Infectious Diseases, the Administration on Aging, the National Center for Health Services Research and Health Care Technology, the Health Care Financing Administration, and the Veterans Administration. To optimally coordinate efforts among these major programs a Secretarial Task Force was established in the Department of Health and Human Services. This Task Force, Chaired by the Assistant Secretary for Health, involved representatives of all these agencies as members in addition to the Surgeon General and the Assistant Secretary for Planning and Evaluation. In 1986, through Congressional action, the Task Force became legislatively established as the *Council on Alzheimer's Disease*, with the same members. In addition, a non-federal *Advisory Panel on Alzheimer's Disease* was also established by Congressional action. The Panel consists of 15 national authorities on Alzheimer's disease selected for their depth and breadth of expertise in this area. The Council and the Panel were designed to work together closely and further reflect the scope of concern and interest that is being focused on Alzheimer's disease. Progress is growing through all of these partnerships.

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This publication was made possible by the
AMERICAN ASSOCIATION FOR
GERIATRIC PSYCHIATRY (AAGP)
P.O. Box 376A, Greenbelt, Maryland 20770